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From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing  
(day/month/year) 09.11.1999

Applicant's or agent's file reference  
H0535/7007WO

**REPLY DUE** within 3 month(s)  
from the above date of mailing

International application No.  
PCT/US99/01193

International filing date (day/month/year)  
20/01/1999

Priority date (day/month/year)  
20/01/1998

International Patent Classification (IPC) or both national classification and IPC  
C12Q1/52

Applicant  
GREEN, Howard et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

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**NOV 23 1999**

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3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

**If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20/05/2000.

Name and mailing address of the international preliminary examining authority:



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**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-35 as originally filed

**Claims, No.:**

1-76 as originally filed

**Drawings, sheets:**

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 1-52,

because:

- ☒ the said international application, or the said claims Nos. 1-52 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Claims	1-73: yes
Inventive step (IS)	Claims	1-73: yes
Industrial applicability (IA)	Claims	53-73: yes

**2. Citations and explanations**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

1). Preliminary remark

Reference is made to the following document cited in the international search report:

D1: US-A-5 773 577

2). Comments with regard to item III

- a) Claims 1-52 which are directed to methods of treatment of the human or animal body relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
- b) For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3). Comments with regard to item V

a) Novelty

None of the various aspects of the claimed invention appear to be disclosed in the relevant state of the art (see the non-intermediate document cited in the international search report). Therefore, it can be acknowledged that the claimed subject-matter as a whole is new, in accordance with the requirements of Article 33(2) PCT.

b) Inventive step

- (i) The technical problem solved by the invention may be regarded as the provision of means for attaching agents, such as a cosmetic agent, a bulking agent, a coloring agent or a pharmaceutical agent to a body tissue.
- (ii) The solutions proposed in the claims rely on the use of **transglutaminase** acting on a linking molecule. They appear not to be suggested in the relevant state of the art. Therefore, it can be acknowledged that the claimed subject-matter as a whole involves an inventive step, in accordance with the requirements of Article 33(3) PCT.

c) Document D1 cited as a P-Document

If it appeared that the priority were not valid document D1 should be taken into consideration when examining whether the claimed subject-matter is new and involves an inventive step.

4). Comments with regard to item VIII

- a) The expression "*a non-corneocyte, nonlabeling agent*" as used in claim 1 lacks clarity, contrary to article 6 PCT:
  - (i) From the description (see page 2, lines 10-14) it can be derived that it has been intended to specify that the agent to be fixed is not a corneocyte protein. The aforementioned expression should be reformulated to accurately account for this technical feature.
  - (ii) As according to a particular embodiment the agent can be a coloring agent (see page 5, line 3), i.e., an agent which could be used as a label, the term "*nonlabeling*" appears to be ambiguous.
- b) It is not clear from the description, contrary to Article 6 PCT, why the

- restriction introduced by the Applicants in claim 1 as regards the agent to be fixed to a body tissue, should not also apply to independent claims 20 and 32. In this respect, the mere statement on page 5, lines 24-28 is not regarded as being convincing.
- c) Each of claims 43 and 44 fails to specify the steps which are essential to the performance of the respective claimed methods. Said steps are only mentioned in dependent claim 45. Therefore, claims 43 and 44 are objected to under article 6 PCT.
  - d) Also claim 53 lacks clarity, contrary to Article 6 PCT, as according to a particular embodiment mentioned in the claim the nonlabeling agent referred to therein could be a coloring agent, i.e., an agent which could serve the purpose of labeling a structure.